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The Ipsilateral Human Motor Cortex Can Functionally Compensate for Acute Contralateral Motor Cortex Dysfunction

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Summary

What promotes motor recovery from stroke? To date, studies of recovery from stroke have shown alterations in function in various cortical areas, including the contralesional (unaffected) motor cortex (M1) [1–5]. However, whether these changes contribute to recovery or are mere epiphenomena remains unclear [6, 7]. We therefore sought evidence that the ipsilateral M1 can compensate for dysfunction of the contralateral M1. We recorded the change in force production during a finger-tapping task in response to acute disruption of M1 function by repetitive transcranial magnetic stimulation (rTMS). Neither control (occipital) nor ipsilateral M1 rTMS lead to a change in tapping force. RTMS over contralateral M1 had a short-lived effect and induced changes in ipsilateral M1 excitability around the time that these behavioral effects abated, consistent with delayed compensation by the ipsilateral M1. Simultaneous bilateral M1 stimulation, designed to prevent compensation by the ipsilateral M1, had a large and prolonged effect on tapping force. This is the first demonstration that the ipsilateral primary motor cortex is capable of functionally significant compensation for focal contralateral cortical dysfunction in the adult human and provides a rational basis for interventional treatments aimed at promoting functional compensation in unaffected cortical areas after stroke.

Results and Discussion

It remains unclear whether changes in contralesional M1 function after mono-hemispheric stroke are mechanistically related to motor recovery [1–4]. Imaging studies have shown that greater ipsilateral compared to contralateral M1 activation occurs early, prior to substantial motor recovery, and that improvements in the affected hand's performance with intensive training are associated with reversal of this ratio [1, 5], although this remains controversial [6]. Similarly, although TMS shows that ipsilateral changes in M1 function are more frequent after stroke, these are reversed in concert with motor recovery [7–10]. Overall, these studies suggest either that ipsilateral M1 activation represents a compensatory mechanism, later replaced by other processes, or that it is spurious, perhaps due to mirror movements or unmasking of circuitry that is normally suppressed and has nothing to do with motor recovery [7].

We therefore sought evidence that ipsilateral M1 can compensate for dysfunction of contralateral M1 by testing subjects' ability to control the force of a fractionated finger movement, the type of movement most impaired after motor stroke. However, rather than studying stroke patients, we used 5 Hz rTMS to elicit controlled, temporary, and partial disruption of M1 function in healthy humans. Such trains are known to increase cortical excitability for short periods beyond the duration of stimulation [11, 12]. Thus, we expected tapping force to increase temporarily after 5 Hz stimulation. We hypothesized that acute disruption of M1 function would have only a modest, short-lived behavioral consequence on contralateral limb performance because the unstimulated M1 helps compensate for the deficit. This hypothesis generates two important predictions. First, there should be physiological evidence of changes in the unstimulated ipsilateral M1 *following* rTMS. These changes should favor inhibitory mechanisms if they are to have compensatory potential. Second, the effect of bilateral stimulation should exceed the algebraic sum of the behavioral effects of separate right and left unilateral stimulation because a normal functioning ipsilateral M1 is no longer available to compensate.

Seven healthy right-handed volunteers were studied. Paced at 1 Hz by a metronome, subjects tapped a strain gauge with their right index finger (Figure 1A). After a period of practice, subjects were consistently able to deliver a target force of 0.1 Newtons. Figure 1B shows the effects of a 30 s train of 5 Hz rTMS applied at 90% of the active motor threshold (AMT) to different cortical sites on the force of finger taps made in a representative subject. RTMS to any of these cortical sites failed to evoke overt muscle twitches or EMG responses in the contralateral finger, confirming its subthreshold nature. This low stimulation intensity was further confirmed by the absence of transcallosal facilitation or inhibition of tonic ipsilateral EMG activity during rTMS. Figure 1C shows the cumulative sums (cusums) of the percentage difference between the prestimulation mean peak force and consecutive peak forces of finger taps averaged across all seven subjects. There was no significant change in tapping force with ipsilateral (right) M1 or control occipital stimulation. However, there was a modest increase in tapping force with stimulation of the contralateral M1. Subsequent change point analysis confirmed that tapping force became inappropriately elevated after rTMS was delivered to the contralateral M1. This effect began 8 s after the offset of stimulation and lasted 43 s.

Strikingly, simultaneous bilateral stimulation of both motor cortices had a large effect on tapping force. Beginning during stimulation and lasting 110 s, this effect outlasted both contralateral (left) rTMS and the algebraic sum of separate stimulation of the right and left M1 (Figure 1C). Figure 1D confirms that the elevation in

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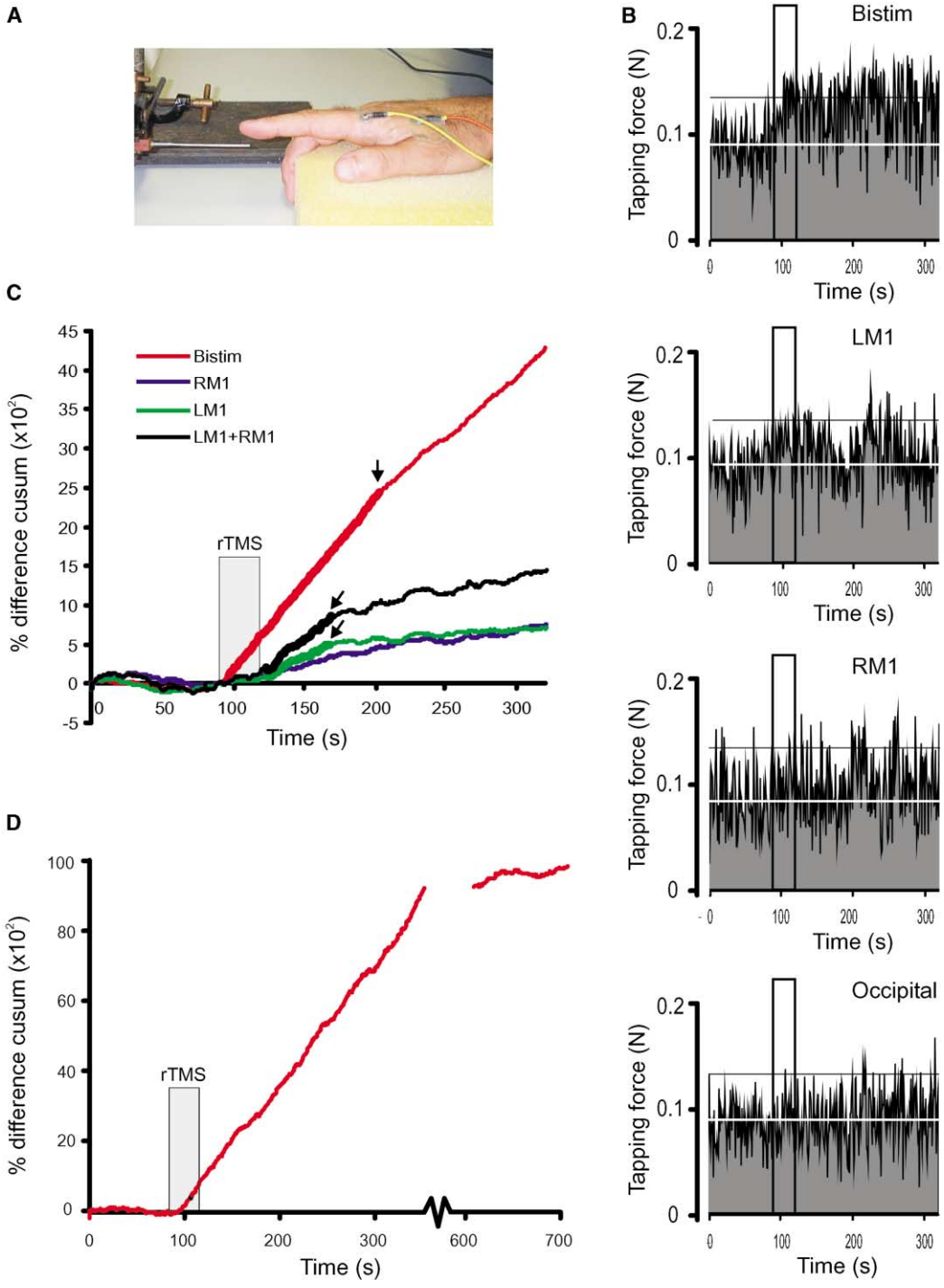

Figure 1. Behavioral Effects of rTMS

(A) Tapping set-up.

(B) Data from one subject shows the effect of rTMS on the force of successive finger taps made with the right forefinger. Stimulations over both motor cortices simultaneously (Bistim), left motor cortex (LM1), right motor cortex (RM1), and occipital cortex (occipital) are shown as boxed areas. The horizontal white line shows the prestimulation mean, and the horizontal black line above this is twice the standard deviation. There is a clear increase in tapping force with simultaneous bilateral stimulation of the motor cortices, and there is no significant change with control occipital rTMS.

(C) Average cusums ($n = 7$) of the percentage difference in peak force compared to baseline, with effects of occipital stimulation subtracted. Those periods of change identified by change point analysis are plotted as broader lines, and their terminations are indicated by arrows. The tapping force became inappropriately elevated after rTMS was delivered to LM1 from 8 s (95% confidence limits 1–21 s) to 51 s (43–63 s) after rTMS. RM1 stimulation did not elicit any significant change, and the algebraic sum of the effects of rTMS over the contralateral and ipsilateral motor cortices (LM1 + RM1) had the same onset and duration as the effect of contralateral stimulation alone. The effect of simultaneous bilateral stimulation of both motor cortices began during stimulation and continued until 86 s (69–102 s) after rTMS.

(D) Cusum of the percentage difference in peak force compared to baseline (without occipital effects removed) after simultaneous bilateral rTMS of both motor cortices in one subject. Recovery is delayed but occurs without further training with visual feedback.

tapping force after bilateral rTMS was temporary and reversed without further training with visual feedback. Change point analysis documented the duration of changes in tapping force (Figure 1D) but did not determine whether there were significant differences in the degree of change in tapping force between stimulation at different sites. This was analyzed by a repeated-measures general linear model (GLM) concentrating on those periods before and after rTMS that were free from any distracting effects of stimulation. The mean peak tapping force prior to rTMS was compared with the two post-rTMS periods defined by change point analysis for the three stimulation conditions (left; right; simultaneous bilateral stimulation). The first of the post-rTMS candidate time periods was the 8–51 s post-rTMS period, over which change point analysis indicated a significant effect from stimulation of the contralateral (left) M1. The second was the remaining period over which change point analysis indicated that only simultaneous bilateral stimulation was still effective (from 52 s to 85 s after the offset of stimulation). Significant main effects were confirmed for time ($F[2, 12] = 7.088$, $p = 0.009$) and stimulation region ($F[2, 12] = 10.842$, $p = 0.015$), and there was an additional interaction between time and stimulation region ($F[4, 24] = 9.410$, $p = 0.007$). A second GLM was performed with the factors time (pre, post 1, post 2 as before) and stimulation region (simultaneous bilateral stimulation; summed separate left and right stimulation). Again, there was a main effect of time ($F[2, 12] = 7.088$, $p = 0.009$), a main effect of region ($F[1, 6] = 6.274$, $p = 0.046$), and an interaction between time and region ($F[2, 12] = 6.036$, $p = 0.015$). Post-hoc tests demonstrated that over the first post-rTMS period the effects of both left M1 stimulation and simultaneous bilateral stimulation were different from effects before rTMS ($p = 0.022$ and $p = 0.018$, respectively). However, this was only true of simultaneous bilateral stimulation for the second period after rTMS ($p = 0.018$), when the effects of simultaneous bilateral stimulation were also greater than those of left stimulation or summed separate left and right rTMS ($p = 0.014$ and $p = 0.023$, respectively). Right M1 stimulation did not have a significant effect on tapping force.

In light of the above, we considered the possibility that the dramatic and prolonged behavioral effects of bilateral compared to contralateral rTMS arose because the ipsilateral M1 was blocked from compensating for the contralateral M1 dysfunction. In this formulation, compensatory change by the ipsilateral M1 would be expected to be maximal over the period beginning 50 s after the offset of rTMS, when compensation reverses the behavioral effects of contralateral stimulation alone. Also, any compensatory change in the ipsilateral M1 would be expected to favor inhibition to counter the local excitatory effects of contralateral 5 Hz rTMS and the resultant increase in tapping force. This is analogous to the balancing effect between the excitability of the two motor cortices observed after monohemispheric stroke [13].

Therefore, we delivered paired-pulse TMS to the right M1 and recorded motor-evoked potentials (MEPs) in the resting left hand before and after rTMS to the left M1. Three conditions were tested. In the first, subjects sat at rest throughout the experiment (henceforward termed RRR). In the second, subjects performed the finger-tapping task with their right hand and tapped throughout both the MEP recordings and rTMS (TTT). In the third, subjects were required to tap only during rTMS and remain at rest during the MEP recordings (RTR). We entered MEP data for the seven subjects into a GLM by using within-subject factors of time (before and after 0–50 s, after 51–100 s) and condition (RRR, TTT, RTR). For the control MEP data, there was a main effect of condition ($F[2, 12] = 7.292$, $p = 0.008$) and a significant interaction between time and condition ($F[4, 24] = 4.030$, $p = 0.012$). Post-hoc tests on the control MEP data confirmed a significant reduction in mean control MEP size in the 51–100 s (but not 0–50 s) after rTMS ($p = 0.008$), when subjects were tapping throughout (TTT) (Figure 2). This effect disappeared at longer intervals. There was no significant change in MEP size when subjects were at rest in the RRR and RTR conditions. The latter demonstrated that delayed effects necessitated continuing task performance and were not a passive effect of rTMS, whether applied to the hemisphere when resting or active.

Our results show that independent stimulation of the contralateral motor cortex had a short-lived effect on the control of fine finger movements, whereas ipsilateral stimulation had no effect at all. In contrast, simultaneous bilateral stimulation of the primary motor cortex had a prolonged and stronger effect that exceeded the algebraic sum of individual contralateral and ipsilateral stimulation. In addition, high-frequency stimulation of the motor cortex contralateral to the tapping hand was associated with a delayed and temporary reduction in *ipsilateral* cortical excitability. These distant effects of rTMS are in keeping with positron emission tomography evidence showing that trains of subthreshold 5 Hz rTMS over one primary motor cortex lead to persisting increases in activity over both primary motor cortices [14].

How could bilateral stimulation have produced a super-additive effect? One possibility is direct potentiation of the effects of bilateral rTMS through temporal summation after convergence on one structure. However, consideration of candidate sites for temporal summation makes this explanation unlikely. There was no evidence of transcallosal effects at the stimulation intensities used in this study, so greater stimulation of the contralateral (left) M1 through additional direct activation of transcallosal inputs to this hemisphere seems unlikely. Of course, this is not to say that adaptive compensation did not involve transcallosal pathways (vide infra and [13]). Temporal summation at a subcortical level seems equally unlikely. We deliberately used low-intensity shocks. Thus, shocks failed to elicit a direct response in activated muscle and were at an intensity that does not evoke a descending volley in the corticospinal tract [15], so non-linear interactions in the spinal cord seem improbable. The nature of our task, necessitating fine fractionated finger movements, also makes convergence at the level of the brainstem reticular formation and activation of reticulospinal projections unlikely [16].

Alternatively, could bilateral stimulation have blocked any compensation that ordinarily dictates recovery from the effects of contralateral rTMS? The behavioral results

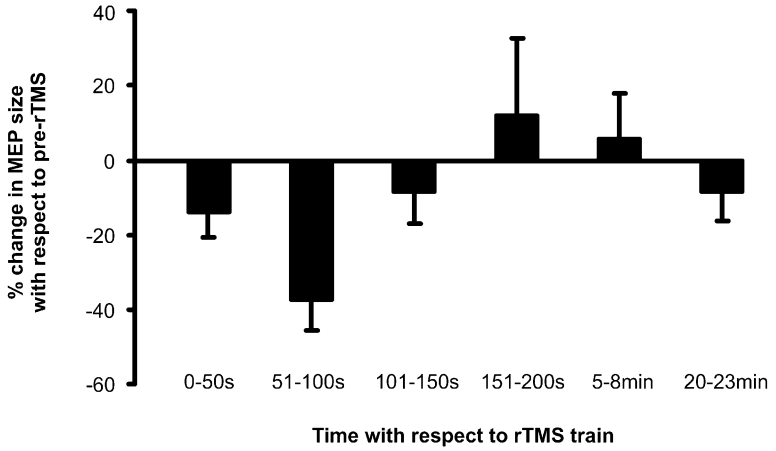

Figure 2. Effects of rTMS on Cortical Excitability

Percentage change in average (n = 7) peak-to-peak control MEP sizes elicited from RM1 with subjects performing the right-handed finger-tapping task after stimulation with 5 Hz rTMS to LM1. The percentage change is with respect to pre-rTMS MEP size. There is a significant reduction in mean MEP size ($p = 0.008$) in the 51–100 s after rTMS. Bars indicate the standard error of the mean.

were compatible with the ipsilateral M1 compensating for the effect of contralateral rTMS. Such an interpretation finds strong support in the cortical-excitability studies. These demonstrated a reduction in ipsilateral cortical excitability during finger tapping in the 51–100 s after contralateral M1 stimulation. Importantly, there was no reduction in cortical excitability ipsilaterally if the subject was at rest after rTMS. This, together with the delayed reduction in excitability when tapping occurred after rTMS, indicates that acute dysfunction of the motor cortex contralateral to the tapping hand may have engendered secondary compensatory change within the ipsilateral M1. This short-term, use-dependent adaptational change [17] only occurred when it was behaviorally relevant, i.e., when the subject was tapping.

Thus, the evidence supports the hypothesis, outlined in the introduction, that the ipsilateral M1 may compensate for the acute dysfunction of the contralateral M1. However, we must also consider the focality of rTMS effects. We deliberately used low-intensity shocks to minimize direct activation of cortical regions other than the target M1. Stimulation may have spread to the primary sensory cortex, but this has little direct motor function. More importantly, given the evidence that activation of the ipsilateral premotor cortex is increased after the motor cortex suffers chronic lesions, such as stroke [6, 18, 19], it is important to consider whether any of the effects of bilateral stimulation could have arisen through direct stimulation of the premotor cortex. This seems unlikely with shocks at the chosen intensity [20]. The nature of the behavioral deficit induced by 5Hz rTMS to the motor cortex also deserves further comment. It involved a selective increase in force without effects on mean movement frequency or the variability of movement frequency. Our effects were temporary and reversed without further training with visual feedback. This suggests that the rTMS did not impair early motor consolidation [21] and did not destroy the motor program or internal model related to the task. Rather, it temporarily disrupted how the motor cortex translated the program/model into desired forces and led to an overestimate of the required force.

What do we mean when we refer to compensation by the ipsilateral (in this case right) motor cortex? There is substantial evidence that both motor cortices are activated in unilateral distal movements, particularly when these are fine or complex [22–24]. One possibility is that compensation occurs through direct ipsilateral corticospinal and indirect descending ipsilateral projections to spinal motoneurones controlling the fingers. However, the anatomical and physiological evidence suggests that such pathways are relatively unimportant in the control of distal upper-limb muscles in primates, including humans [25–27], particularly at low contraction strengths, such as those utilized in the current paradigm [28, 29]. Alternatively, both motor cortices may form a spatially distributed circuit linked through transcallosal and cortico-subcortico-cortical pathways, and this circuit may organize different aspects of movement and may be akin, for example, to the bilateral circuit subserving spatial attention [30]. Movement would then be largely effected by the contralateral M1, but if this function were disturbed, the role of the ipsilateral M1 in this bilateral organization might be increased [31].

Conclusion

This is the first direct demonstration that the ipsilateral primary motor cortex is capable of functionally significant compensation for focal contralateral cortical dysfunction in the adult human. As such, it complements recent findings that the extent of topographical representation of swallowing muscles in ipsilateral motor cortex correlates with recovery of dysphagia after stroke [31] and that the ipsilateral dorsal premotor cortex may also be capable of adaptive compensation after stroke, albeit as assessed by a selective reaction time task [19]. The ability to induce reversible and controlled functional compensation in healthy subjects provides an important model for the screening of treatments for their potential to promote functional compensation in unaffected cortical areas after stroke.

Supplemental Data

Supplemental Results and Experimental Procedures are available with this article online at http://www.current-biology.com/cgi/content/full/13/14/1201/DC1/.

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